Amendment of the G-BA Code of Procedure “Dossier templates”

Kirsten H Herrmann

Friedhelm Leverkus

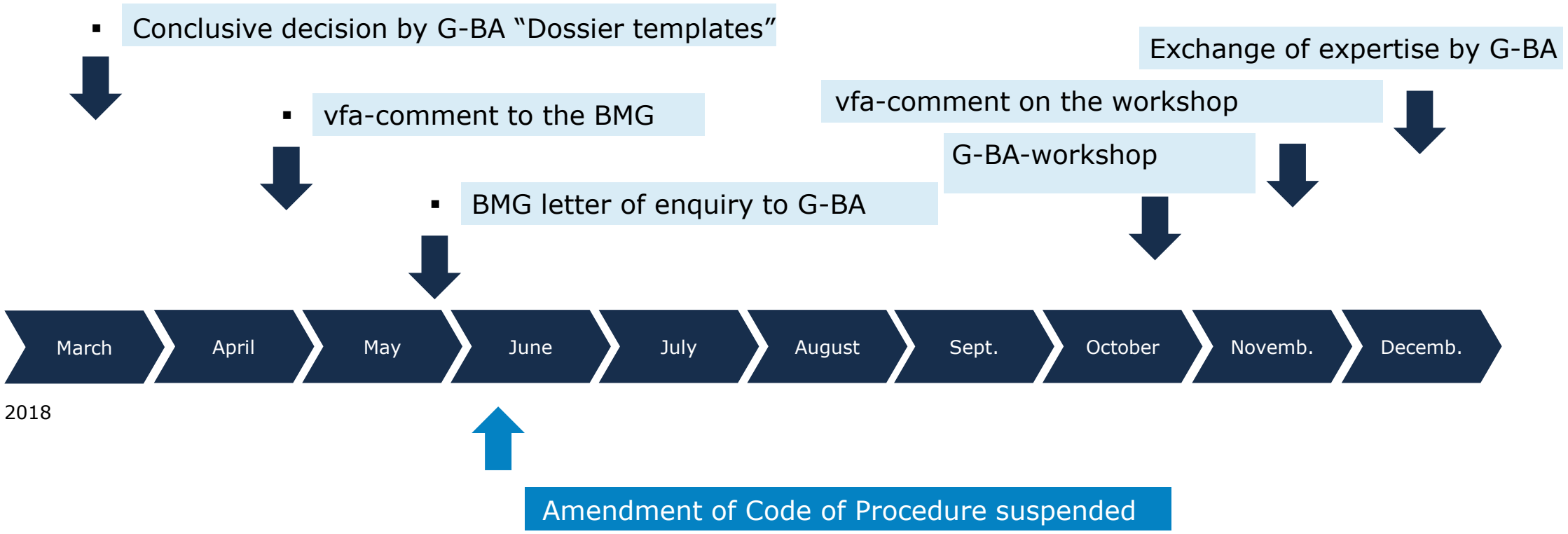
Sebastian Werner

vfa. Die forschenden Pharma-Unternehmen

New dossier templates : main changes- nonadherence may lead to rejection of the dossier

- Patient data listings of study reports
- Data cuts: "Evaluations of individual data cuts for all relevant endpoints collected, even if a data cut was originally planned only for the evaluation of individual endpoints.”
- Survival time analyses and Kaplan-Meier curves with clearly different observation times
- Values in the course of the study, inclusive graphic representation and AUC analyses for PROs
- AE analyses at MedDRA SOC/PT level for (i) AE, (ii) SAE (iii) serious AE, (iv) terminations due to AE, as well as AE differentiated according to severity (e.g. according to CTCAE)
- AE analyses if planned: specific disease concepts (e.g. SMQs or AESI).
- AE-Analyses: if disease-related events are taken into account: additional AE analyses excluding "disease-related" events (e.g. progression, exacerbation)
- All usual subgroup analyses should be submitted for all AE analyses (Annex Module 4).

Amendment of the G-BA Code of Procedure "Dossier templates"



Cooperation of the vfa office with member companies in the preparation of positions and comments

Broad basis
In the preparation of positions and comments, nominated representatives of all member companies concerned shall be involved.

Close exchange
Close cooperation is ensured in vfa committee meetings, own workshops, written exchanges or TCs.

Special knowledge
The representatives of the member companies involve necessary partners within the company in order to make specialist knowledge available (e.g. biostatistics).

Bringing biostat expertise into Vfa positions and statements- Working Party Benefit Assement

- For some issues the vfa Project Group Biostatistic (representatives of member Companies) will be consultated- e.g. CATCER
- Draft Paper bei Vfa (Sebastian , Andrej, Tina)
- Draft is discussen in working party benefit assessment (representatives of HTA departments of member Companies, two members Biostats)
- Representatives coordinate with their company biostats.
- Paper is Approved by working party benefit assessment

vfa-comment to the BMG

Disproportionate additional effort due to new dossier requirements:

1. Additional evaluations

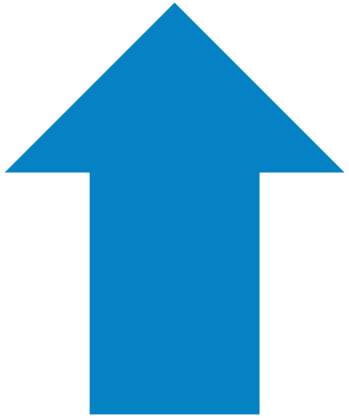
- AE-evaluations
- Data cuts
- Subgroup analyses

2. Patient-specific data

- Compliance with data protection obligations

Estimated effort on average

+ 1000 % evaluations

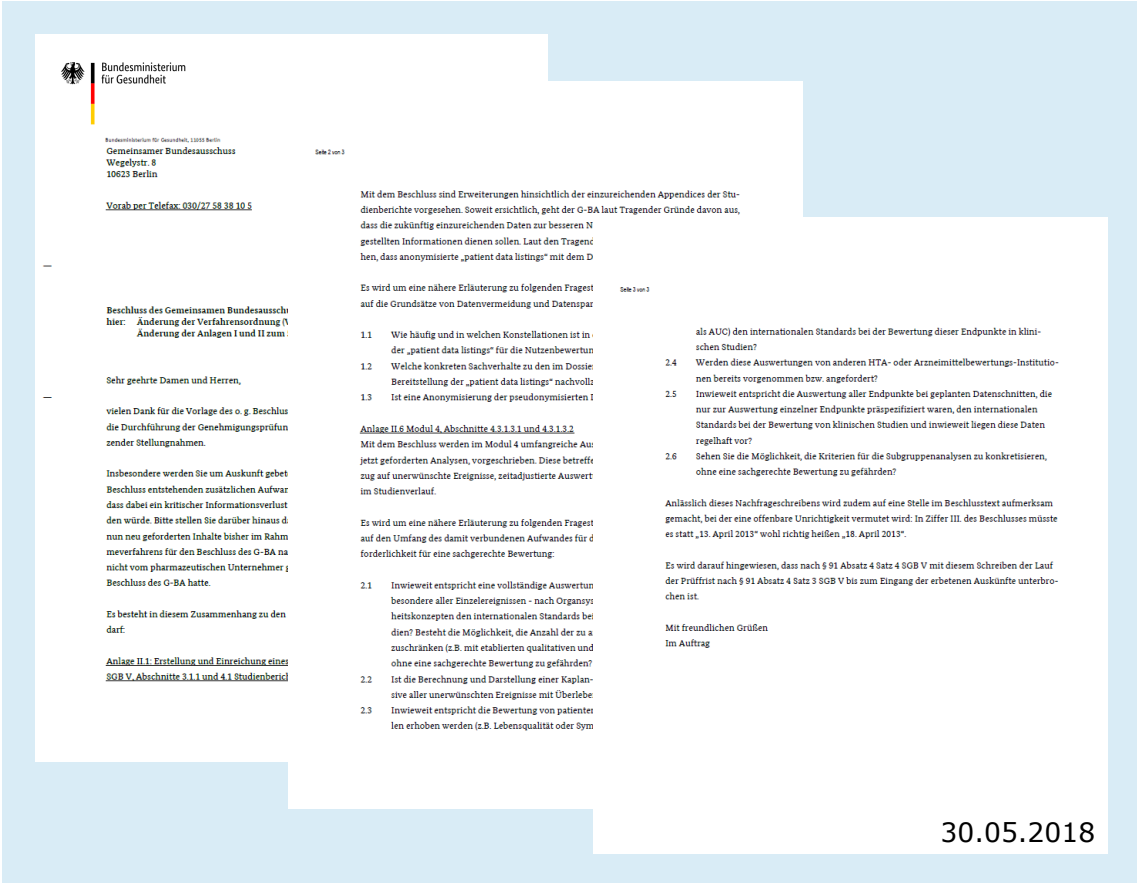


2. Mai 2018

BMG letter of enquiry on the conclusive decision by G-BA

Additional information and complementary comments requested

- Aim: "To demonstrate ways of **reducing** the additional **effort** involved in preparing dossiers without causing a critical loss of information."
- Extensive requirements for information to **document** the **necessity** of the new requirements
- **Procedure suspended** until further notice



Bundesministerium für Gesundheit

Gemeinsamer Bundesausschuss
Wegelystr. 8
10623 Berlin

Vorab per Telefax: 030/27 58 38 10 5

Seite 2 von 3

Sehr geehrte Damen und Herren,

Seite 3 von 3

30.05.2018

G-BA-workshop "Dossier templates" with associations

Gemeinsamer Bundesausschuss

participants: 4 per organisation

Manufacturing associations	Supporting organizations G-BA	Other
vfa	GKV-SV	IQWiG
BPI	KBV	BMG
BAH	DKG	
BIO Deutschland		
PRO Generika		

manufacturing associations

with company representatives

"Explain the background to the adjustments and **discuss the feasibility of the requirements**"

TOP	Topic
1	Patient-specific data
2	Data cuts
3	AE-evaluations
4	Subgroup analyses
5	Other changes

26.10.2018

The positions of the manufacturers' associations were coordinated under the leadership of the vfa.

vfa. Die forschenden Pharma-Unternehmen

G-BA-workshop "Dossier templates" with associations: positions of the industry

1. Patient-specific data is not required.
2. For each individual endpoint, a relevant (meaningful) data section should be submitted (e.g. which was also authoritative in the approval), which can be supplemented by further data sections with justification. A G-BA consultation can be helpful.
3. No change in the status quo of the dossier template for AE-representations that has applied to date.
4. Limit subgroup analyses to "aggregated AE endpoints". No subgroup analyses at SOC/PT level.
5. T2T Event Analysis for Data with different observations time but was seen from Industry as useful

G-BA-workshop "Dossier templates"
Proposals to limit the additional effort

Gemeinsamer Bundesausschuss

Topic	Proposal of the G-BA
Patient-specific data	New legal opinion on data protection
Data cuts	Limiting criteria: "irrelevant" (highly distorted), "without relevant" gain of information
AE-Evaluations	Limiting thresholds for the presentation of evaluations
Subgroup analyses	Limitation of additional analyses (Kaplan-Meier-Plots)

- Constructive discussion without final consensus
- Further opportunity to comments agreed
- Step towards reduction additional effort, but still unsolved problems

vfa-comments to GBA-workshop

The proposals still lead to disproportionate additional effort:

1. Additional evaluations

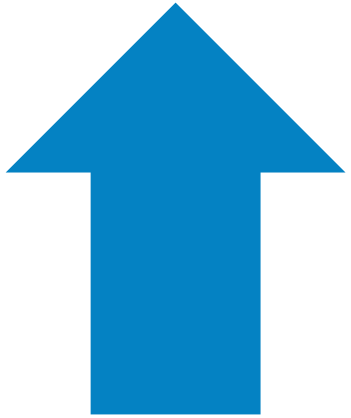
- AE-Evaluations
- Data cuts
- Subgroup analyses

2. Patient-specific data

- Compliance with data protection obligations

Estimated effort On average

+ 450 % evaluations



26. November 2018

1. Patient-specific data

G-BA Data protection Legal opinion:

- “No anonymisation necessary: pseudonymised data may be transmitted"
- The following is a list of the "permitted offence fulfilled" for the "guarantee of high safety and quality standards in health care" pursuant to § 22 Para. 1 No. 1 Letter. c. BDSG , "because § 35 a SGB V with "expediency" and "quality-assured application" also concerns the guarantee of high safety and quality standards in health care".

- Existing legal uncertainty: anonymisation of data still necessary.
- The necessity of the data is not sufficiently demonstrated.

2. Data cuts

Proposal Limiting criteria

- **Irrelevant data cuts** because of too much distortion
  - e.g. Data cuts not planned in advance or not initiated by an external body (regulatory authorities)
  - Follow-up data cuts if previous data cuts were already distorted
- **Data cuts without relevant information gain**

- Indetermination of the control leads to great uncertainty and therefore cannot reduce the additional effort.

3. AE-Evaluations (SOC/PT)

Proposal of limitations:

- Criterion 1: AE events (SOC/PT) if incidence is **at least 10 %** in the study arm
- Criterion 2: SAE events (SOC/PT) if incidence is **at least 5 %** in the study arm
- Criterion 3: Events (SOC/PT) that occur in **at least 10 patients AND at least 1 %** in the study arm (equally for AE, SAE)

- Criterion 3 is unusual threshold and unsuitable to reduce the additional effort relevant, especially in larger studies or in oncological indications.
- No proper differentiation between AE and SAE for criterion 3.

4. Subgroup analyses

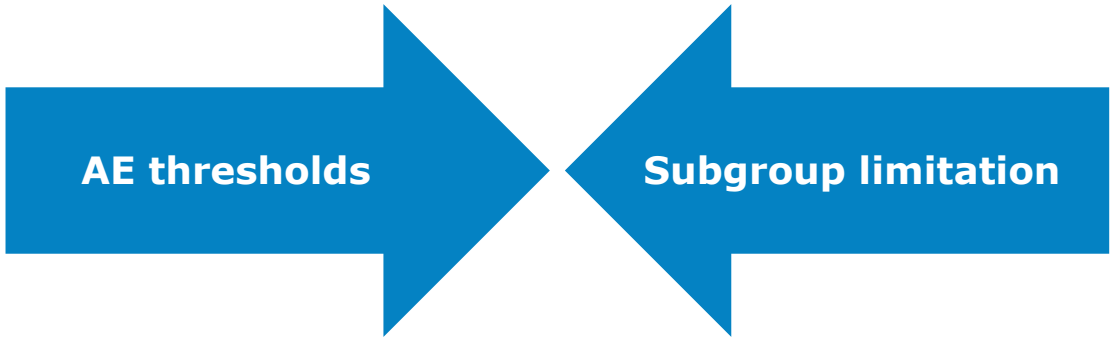
Proposal of limitations:

Criterion Method paper: Application of the threshold of at least 10 persons in each subgroup and at least 10 events in one of the subgroups.

- Kaplan Meier plots for non-significant interaction tests do not have to be submitted.

- No noticeable reduction in additional effort because no limitation was proposed for (AE) endpoints or subgroup characteristics.
- Criterion Method paper does not contribute to the reduction of the additional effort, as it is already valid under currently valid dossier templates.
- Necessity is not sufficiently demonstrated.

Linking consent to thresholds to the condition of a reasonable limitation of subgroups



"The effort correlates not only with the selected threshold level but also with the number of subgroups formed. In order to keep the effort within limits, it is necessary ***to reduce*** *the number of* ***subgroups*** *formed* ***or increase*** *the* ***threshold value*** *accordingly. These two aspects cannot be developed in isolation from each other".*

vfa. Die forschenden Pharma-Unternehmen

Bundesverband der Arzneimittel-Hersteller e.V. B.A.H beraten • analysieren • handeln

Gemeinsamer Bundesausschuss

BPI Bundesverband der Pharmazeutischen Industrie e.V.

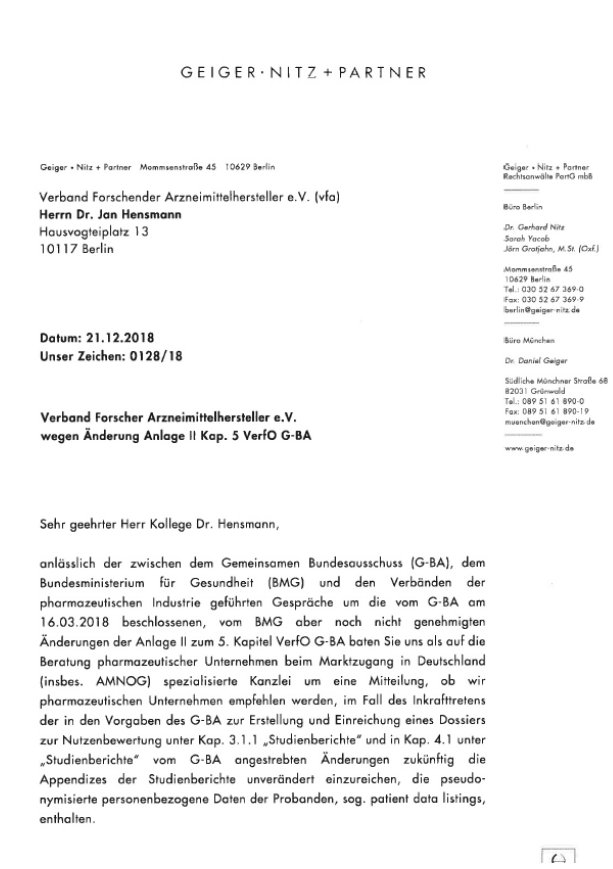
progenerika

G-BA exchange with manufacturers' associations 29 November 2018

Legal opinions on patient-specific data

Overall, the expert opinion confirms the vfa legal opinion already expressed:

- RA Nitz comes to the conclusion that he would advise pharmaceutical companies - under the conditions of the amended Code of Procedure adopted by the G-BA - to anonymise “patient data listings” due to the necessary risk minimisation in view of the applicable data protection regulations and sanctions.



GEIGER · NITZ + PARTNER

Geiger • Nitz + Partner Mommsenstraße 45 10629 Berlin

Verband Forschender Arzneimittelhersteller e.V. (vfa)
Herrn Dr. Jan Hensmann
Hausvogteiplatz 13
10117 Berlin

Datum: 21.12.2018
Unser Zeichen: 0128/18

Verband Forscher Arzneimittelhersteller e.V.
wegen Änderung Anlage II Kap. 5 VerfO G-BA

Sehr geehrter Herr Kollege Dr. Hensmann,

anlässlich der zwischen dem Gemeinsamen Bundesausschuss (G-BA), dem Bundesministerium für Gesundheit (BMG) und den Verbänden der pharmazeutischen Industrie geführten Gespräche um die vom G-BA am 16.03.2018 beschlossenen, vom BMG aber noch nicht genehmigten Änderungen der Anlage II zum 5. Kapitel VerfO G-BA baten Sie uns als auf die Beratung pharmazeutischer Unternehmen beim Marktzugang in Deutschland (insbes. AMNOG) spezialisierte Kanzlei um eine Mitteilung, ob wir pharmazeutischen Unternehmen empfehlen werden, im Fall des Inkrafttretens der in den Vorgaben des G-BA zur Erstellung und Einreichung eines Dossiers zur Nutzenbewertung unter Kap. 3.1.1 „Studienberichte“ und in Kap. 4.1 unter „Studienberichte“ vom G-BA angestrebten Änderungen zukünftig die Appendizes der Studienberichte unverändert einzureichen, die pseudonymisierte personenbezogene Daten der Probanden, sog. patient data listings, enthalten.

Geiger • Nitz + Partner
Rechtsanwälte PartG mbB

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January 2019

Summary

On estimands and the analysis of adverse events in the presence of varying follow-up times within the benefit assessment of therapies

Steffen Unkel[1] | Marjan Amiri[2] | Norbert Benda[3] | Jan Beyersmann[4] | Dietrich Knoerzer[5] | Katrin Kupas[6] | Frank Langer[7] | Friedhelm Leverkus[8] | Anja Loos[9] | Claudia Ose[2] | Tanja Proctor[10] | Claudia Schmoor[11] | Carsten Schwenke[12] | Guido Skipka[13] | Kristina Unnebrink[14] | Florian Voss[15] | Tim Friede[1]

- AMNOG is a learning system
- All parties involved should work together to enhance
- T2T for Data with varying observation time adds effort, but are usefull.
- Subgroup Analyis for all PTs is much effort, but would it relevant for any decision ?
- Looking forward to the G-BA decision at end of February.

European Statistical Meeting

Latest Trends in Health Technology Assessments (HTA)

Friday 15th February 2019
Berlin

Dr. Kirsten H. Herrmann, Amgen GmbH,

Is there a need of additional International Standards?

PRO, HRQoL, MID

This presentation represents the personal view of the author and may not be representative for Amgen GmbH

SISAQOL Consortium

SISAQOL Consortium

- directed by the European Organization for Research and Treatment of Cancer (EORTC)
- to develop guidelines and recommendations to standardize analyses of PRO data in cancer RCTs.

Measures of HRQOL and PROs are key in comparative risks and benefits assessments of cancer therapies and fostering patient-centered cancer care.

Lack of consensus on how HRQoL/ PRO measures in cancer RCTs are analyzed and interpreted

Perspective Regulators:

- reservations about the conclusions drawn from PRO data to date.
- poorly defined research objectives and hypotheses
- lack of rigorous standards in analyzing PRO data

Perspective from Patients

- Crucial: clear communication between the patient and the stakeholders involved in treatment on risks, benefits, and potential side effects
- missing PRO data provided a clear opportunity for possible patient participation

MID EORTC Quality of Life

- the size of a difference in a QoL score that would be comparable to a change normally considered by clinicians as relevant
- to estimate disease specific MIDs for the most widely used cancer specific questionnaire (the EORTC-QLQ-C30) which will aid interpreting QOL scores in a manner that is clinically meaningful to doctors and patients
- This project will supplement previously published MID guidelines research by using individual patient data to estimate MIDs for different cancer sites separately, hence, further providing evidence to robust and practical MID guidelines for the EORTC QLQ-C30.

What:

- meaningful interpretations to aggregated HRQOL scores
- HRQOL scores between groups
- within-patient changes in HRQOL over time
- Determining what represents a **minimally important difference (MID)** in HRQOL scores is useful to clinicians, patients and researchers
- benchmark for assessing the success of a new healthcare intervention or the design of future clinical trials (e.g., determining sample sizes).

Why:

- to establish MIDs for all QLQ-C30 scales according to cancer sites, using individual patient data from archive EORTC trials.

How:

- anchor-based approach and relies on constructing clinical anchors using available clinical variables
- A disease-oriented and methodological panel provide independent guidance on anchor selection
- how the estimated MIDs compare with previously published guidelines
- contributing to robust MID guidelines for the EORTC QLQ-C30

Relevance for Patients

- how much better should the score given by a patient be in order to influence decision about treatment
- manuscript on MIDs for adjuvant melanoma is in preparation
- publication of other disease specific MIDs e.g., head and neck, breast and prostate cancer.
- to continually disseminate results in international conferences such as ASCO and ISOQOL

Benefit assessment and HTA Findings

- IQWiG criticisms with reference to "current discussion on methods" - Development of quality standards for MID validation studies
  - no anchor-based procedure or lack of suitability of the anchor (not asked of the patient, low correlation)
  - no longitudinal study
  - no prespecification
  - non-comparable patient population
  - no clearly specified MID
  - no response criteria for the present indication
- G-BA follows IQWiG's criticism with few exceptions in existing practice (FKSI-DRS, EQ-5D VAS, SF-36)
- G-BA with own critical evaluation

Assessments AMNOG: Responder Analysis not accepted

Report	Instrument	IQWiG accepted	G-BA accepted
Cabozantinib (decision 05.04.2018)	FKSI-DRS	no	yes
Tivozanib	FKSI-DRS	no	yes
Dupilumab	Patient Oriented Eczema Measure (POEM)	no	no
Abirateronacetat	Impairment by Fatigue (BFI Items 4 a–f)	no	no
	Impairment by pain (BPI-SF Items 9 a–g)	no	no
	Schmerzintensität/intensity of pain (BPI-SF Items 3–6)	no	no
Brentuximab Vedotin (decison 05.07.2018)	Skindex-29	-	no
Ocrelizumab	Multiple Sclerosis functional Composite (MSFC)	no	no
	mFIS	no	no
	EQ-5D VAS	no	no
	SF-36	no	yes
Letermovir	FACT-BMT	-	no
Fluticasonfuroat/Umeclidinium/Vilanterol	TDI Focal Score	no	no
Fluticasonfuroat/Vilanterol-Trifenatat (Decision 02.08.2018)	AQLQ(S)	-	no
Insulin glargin/Lixisenatid	EQ-5D VAS	no	no
Ixekizumab (decision 16.08.2018)	SF-36	no	no
Cariprazin	PANSS	no	no
Extrakt aus Cannabis sativa (decision 01.11.2018)	Schmerz durch Spastik/ Numerical Rating Scale (NRS)	no	no
	SF-36	no	no
	Aktivitäten des täglichen Lebens/ Activities of daily life (Barthel-Index)	no	no
Bosutinib (decision 22.11.2018)	EQ-5D-VAS	no	yes
Olaparib (decision 06.12.2018)	EQ-5D-VAS	no	yes
	FACT-O	no	no
Bictegravir / Emtricitabin / Tenofoviralafenamid	SF-36	no	no
Velmanase alfa	CHAQ	-	no
Ipilimumab, Nivolumab (decision 20.12.2018)	EQ-5D-VAS	no	yes

Acknowledgement

Thanks to
Dr. Sebastian Werner,
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